

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appln. No. :10/601,968 Confirmation No.:8810
 Patent No. :7,268,149
 Applicant :Fensome et al.
 Filed :June 23, 2003
 Issued :September 11, 2007
 TC/A.U. :1614
 Examiner :Kwon, Brian
 Customer No. :38199
 Title : Cyclothiocarbamate Derivatives as Progesterone Receptor
 Modulators and Methods of Treating Skin Disorders

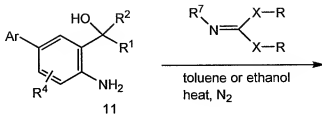
Attention: Certificate of Corrections Branch
 Commissioner for Patents
 PO Box 1450
 Alexandria, VA 22313-1450

REQUEST FOR CERTIFICATE OF CORRECTION
UNDER 35 USC § 254

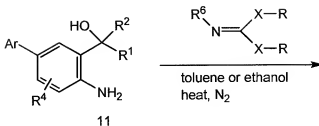
Sir:

The following errors were found in the above-identified patent.

- (1) Col. 4, line 54, replace "C to C₃" with -- C₁ to C₃ --.
- (2) Col. 18, Scheme VII, lines 5-12, replace the following reaction:



with the following reaction:



- (3) Col. 36, line 28, replace "VII" with -- μ l --.
- (4) Col. 42, line 12, replace "manual" with -- mammal --.

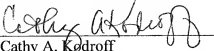
It is requested that a Certificate of Correction be issued to correct the above errors in accordance with the enclosed forms, which are submitted herewith.

Because all errors were made by the US Patent and Trademark Office (USPTO), no fee is due for correction of these errors. To support Applicants' assertion that these are USPTO errors, Applicants have enclosed a copy of the original specification pages as filed which contain the correct language for errors (1) - (3) noted above. The correct language in these original specification pages is identified by a handwritten bolded box.

Error four (4) was also a typographical error on the part of the USPTO. To support this assertion, Applicants' have enclosed a copy of page four (4) of the 37 CFR 1.312 Amendment filed on June 5, 2007 which contains the correct language for original claim 33, issued claim 8.

The director of the US Patent and Trademark Office is hereby authorized to charge any deficiency in any fees due with the filing of this paper or credit any overpayment in any fees paid on the filing, or during prosecution of this application to Deposit Account No. 08-3040.

Respectfully submitted,
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Attorneys for Applicant

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UNITED STATES PATENT AND TRADEMARK OFFICE CERTIFICATE OF CORRECTION

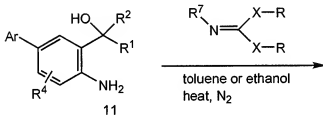
PATENT NO. 7,268,149
APPLICATION NO. 10/601,968
ISSUE DATE. September 11, 2007
INVENTOR(S). Fensome et al.

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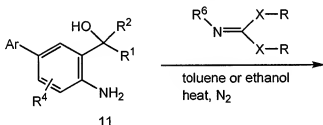
It is certified that an error appears or errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

(1) Col. 4, line 54, replace "C to C₃" with -- C₁ to C₃ --.

(2) Col. 18, Scheme VII, lines 5-12, replace the following reaction:



with the following reaction:



(3) Col. 36, line 28, replace "VII" with -- μ l --.

(4) Col. 42, line 12, replace "manual" with -- mammal --.

MAILING ADDRESS OF SENDER (Please do not use customer number below):

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This collection of information is required by 37 CFR 1.322, 1.323, and 1.324. The information is required to obtain or retain a benefit by the public, which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C 122 and 37 CFR 1.14. This collection is estimated to take 1.0 hour to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Attention Certificate of Corrections Branch, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

R^G is selected from the group consisting of H, C_1 to C_3 alkyl, and substituted C_1 to C_3 alkyl;

R^6 is selected from the group consisting of H, C_1 to C_3 alkyl, and C_1 to C_4 CO_2 alkyl;

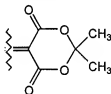
Q^1 is selected from the group consisting of S, NR^7 , and CR^8R^9 ;

R^7 is selected from the group consisting of CN, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_3 to C_8 cycloalkyl, substituted C_3 to C_8 cycloalkyl, aryl, substituted aryl, carbon-based heterocyclic ring having in its backbone 1 to 3 heteroatoms, substituted carbon-based heterocyclic ring having in its backbone 1 to 3 heteroatoms, SO_2CF_3 , OR^{11} , and $NR^{11}R^{12}$;

R^8 and R^9 are independent substituents selected from the group consisting of H, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_3 to C_8 cycloalkyl, substituted C_3 to C_8 cycloalkyl, aryl, substituted aryl, carbon-based heterocyclic ring having in its backbone 1 to 3 heteroatoms, substituted carbon-based heterocyclic ring having in its backbone 1 to 3 heteroatoms, NO_2 , CN, and CO_2R^{10} ;

R^{10} is selected from the group consisting of C_1 to C_3 alkyl and substituted C_1 to C_3 alkyl;

or CR^8R^9 comprise a six membered ring having the structure:

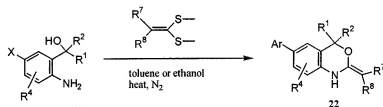


R^{11} and R^{12} are independently selected from the group consisting of H, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, aryl, substituted aryl, carbon-based heterocyclic ring having in its backbone 1 to 3 heteroatoms, substituted carbon-based heterocyclic ring having in its backbone 1 to 3 heteroatoms, acyl, substituted acyl, sulfonyl, and substituted sulfonyl.

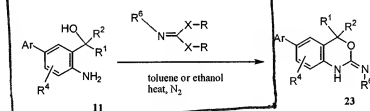
In another embodiment, the compound is of formula I:

20 or 21 is alkylated with an appropriate alkylating agent such as the Meerwein reagent in a suitable solvent such as methylene chloride. This is then followed by a nucleophilic replacement of an appropriate nucleophile such as carbon anion or an amine base to give compounds 22 or 23, which can produce either tautomeric form of compounds 22 or 23.

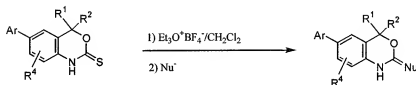
Scheme VI



Scheme VII

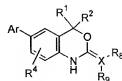


Scheme VIIa



20 or 21

Specific Examples



22, X=C
23, X=N,
R₉ or R₉ = none

compounds were added in the presence of 1 nM progesterone. The cells were incubated at 37°C in a 5% CO₂/humidified atmosphere for 24 hr.

d. *Alkaline Phosphatase Enzyme Assay:*

At the end of treatment, the medium was removed from the plate and fifty μ l of assay buffer I was added to each well. The plates were shaken in a titer plate shaker for 15 min. Then 150 μ l of assay buffer II was added to each well. Optical density measurements were taken at 5 min intervals for 30 min at a test wavelength of 405 nM.

e. *Analysis of Results: Analysis of dose-response data*

For reference and test compounds, a dose response curve is generated for dose (X-axis) vs. the rate of enzyme reaction (slope) (Y-axis). Square root-transformed data are used for analysis of variance and nonlinear dose response curve fitting for both agonist and antagonist modes. Huber weighting is used to downweight the effects of outliers. EC₅₀ or IC₅₀ values are calculated from the retransformed values. JMP software (SAS Institute, Inc.) is used for both one-way analysis of variance and non-linear dose response analyses in both single dose and dose response studies.

f. *Reference Compounds:*

Progesterone and trimegestone are reference progestins and RU486 is the reference antiprogestin. All reference compounds are run in full dose response curves and the EC₅₀ or IC₅₀ values are calculated.

R^3 is H;

R^4 is H;

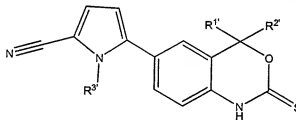
R^5 is a five membered carbon-based heterocyclic ring having in its backbone 1, 2, or 3 NR^6 heteroatoms and having one or two independent substituents selected from the group consisting of H, halogen, and CN;

R^6 is selected from the group consisting of H, C_1 to C_3 alkyl, and C_1 to C_4 CO_2 alkyl;

Q^1 is S;

or a pharmaceutically acceptable salt.

33(Previously Presented). A method of treating acne or hirsutism in a mammal comprising administering to said mammal in need thereof a composition comprising an effective amount of a compound of formula I represented by the structure:



wherein:

$R^{1'}$ is selected from the group consisting of methyl, ethyl, and trifluoromethyl;

$R^{2'}$ is selected from the group consisting of methyl, ethyl, and trifluoromethyl; or

$R^{1'}$ and $R^{2'}$ are joined to form a spirocyclic ring containing 3 to 7 carbon atoms;

and

$R^{3'}$ is C_1 to C_4 alkyl;

or a pharmaceutically acceptable salt thereof to treat said acne or hirsutism.

34(Currently Amended). The method according to claim 33, wherein said compound is 5-(4-ethyl-4-methyl-2-thioxo-1,4-dihydro-2H-3,1-benzoxazin-6-yl)-1-methyl-1H-pyrrole-2-carbonitrile, 5-(4,4-diethyl-2-thioxo-1,4-dihydro-2H-3,1-benzoxazin-6-yl)-1-methyl-1H-pyrrole-2-carbonitrile, 1-methyl-5-(2-thioxo-1,4-dihydrospiro[3,1-benzoxazine-4,1'-cyclobutan]-6-yl)-1H-pyrrole-2-carbonitrile 1-